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10/030,504	03/04/2002	Andre R. Miserez	0796/66513	9130

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,504	MISEREZ, ANDRE R.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 32-61* is/are pending in the application.

4a) Of the above claim(s) *10 and 37-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/08/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, now claims 32-36 in the reply filed on January 30, 2004 is acknowledged. Claims 10 and 37-61 are withdrawn from further consideration. The traversal is on the ground(s) that there is no burden in searching additional sequences. This is not found persuasive because each additional sequence requires significant additional effort both in the many hours of computer time devoted to sequence searching by the Scientific and Technical Information Center and the analysis required by the examiner. Therefore, the restriction requirement is maintained since there is a significant burden in examining multiple sequences.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

2. The drawings are objected to because they contain German in figure 3. The drawings must be in English. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary

to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 32-34 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Because of the use of open claim language and because the claims do not recite a purity or isolated limitation, the claims read on the native sequence found in humans. The native DNA is a product of nature and is not patentable. This rejection may be overcome by amendment of the claims to recite e.g. "an isolated and purified oligonucleotide consisting of".

Claim Rejections - 35 USC § 112 – Second Paragraph

5. Claims 32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 32, it is vague and indefinite how a polymorphism comprises SEQ ID NO: 3, since a polymorphism refers to an alteration in a sequence, and not a sequence itself. For example, SEQ ID NO: 3 comprises one allele of the SREBF-1 (also termed

SREBP-1) gene. To properly identify a polymorphism, the terminology used is G10C (for example if the polymorphism was at nucleotide 10 of the sequence of interest). The use of the term "polymorphism" when referring to an entire sequence renders the scope of the claim indefinite, since it is not clear what constraints are imposed by the use of the term "polymorphism".

In claim 34, the phrase "XmnT" is not clear because "XmnT" is not mentioned in the specification and is not a recognized restriction enzyme. It is likely that this is a typographical error and the enzyme "Xmn I" is meant, but if not, the claim is indefinite over the phrase "XmnT".

Claim Rejections - 35 USC § 112 – Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed

by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

The current claims are drawn to "polymorphisms" which are "characteristic for an increased or decreased risk for hypercholesterolemia in humans" where the polymorphism comprises "SEQ ID NO: 3". The sequence being claimed, SEQ ID NO: 3 is not itself a polymorphism, but rather is a 19 nucleotide oligomer. The specification discloses in figure 1 that there is a single polymorphism in this 19 mer, a G to C change that alters the restriction site of Xmn I. This disclosure does not provide description for all possible polymorphisms in SEQ ID NO: 3 which may be associated with an altered risk of hyperchosterolemia.

All of the current claims encompass a genus of nucleic acids which comprise SREBP polymorphisms which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification. This large genus is represented in the specification by only two particular (and unrelated) polymorphisms for which data is provided demonstrating an association with the phenotypic trait, hypercholestrolemia. Thus, applicant has express possession of only two particular polymorphisms, in a genus which comprises millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. Even in the narrower dependent claims, such as claim 34, where XmnI is required, no specific polymorphism is named. No structural limitations or

requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with hypercholesterolemia is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition in claim 32 of a polymorphism associated with hypercholesterolemia which lacks any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the two specific polymorphisms, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a polymorphism in the SREBP-1 gene", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a deletion, without any definition of the particular polymorphisms claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise polymorphisms of the SREBP1 or SREBP 2 genes.

Another issue is whether there is any structure function relationship which correlates the function, hypercholesterolemia, with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the function of hypercholesterolemia. In this case, the answer is no, there is no structure given, other than the two specific polymorphisms, which is associated with hypercholesterolemia.

Conceptually, at minimum a polymorphism is a single nucleotide change in a DNA sequence. It may represent a larger change, including a deletion, an insertion or multiple changes, but minimally consists of a single nucleotide change. To describe such a change, both possible nucleotides at the position of interest must be disclosed. It is insufficient to describe a polymorphism as, hypothetically, an Adenine at position 57, because this is not a polymorphism, just a sequence. In order to be a polymorphism, the description must state, for example, a Guanosine for Adenine change at position 57. So the description of a sequence is not a description of a polymorphism, since the sequence alone does not provide the structure of the change that IS the polymorphism.

So instant claim 32, for example, provides no description of any polymorphism whatsoever. Further, the specification provides a description of only two polymorphisms. There is no structure in common between the specific nucleotide change in SREBP-1 and SREBP-2. More importantly, there is no structure in common between the specific change at either of the disclosed polymorphisms and any other polymorphism which may exist. This is because there is nothing in common between having a G to A change at position 57 and having a C to A change at position 93 or a G to T change at position 105 or even having a G to A change at position 33 (all of which are hypothetical changes). Even the G to A change at position 33 shares no structural relationship with the G to A change at position 57 because each of these changes occurs in distinct sequence regions, with distinct effects and with no necessary relationship. So there is no common structure between polymorphisms.

The presence and existence of the two polymorphisms in the SREBP sequence does not even necessarily demonstrate that the SREBP receptor itself is necessarily involved in hypercholesterolemia and consequently, the structure of SEQ ID NO: 3 is not necessarily even relevant. These polymorphisms may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in hypercholesterolemia may be tens of thousands of nucleotides distant from the polymorphisms in the SREBP gene.

Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 – Scope of Enablement

8. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the two demonstrated polymorphisms in the SREBP gene, does not reasonably provide enablement for all polymorphisms in SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to polymorphisms in the SREBP gene which are associated with hypercholesterolemia. The invention is is the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass any polymorphism in a sequence comprising SEQ ID NO: 3. The claims broadly encompasses the polymorphisms in any mammalian patient. This means that the method is broadly drawn to the use, not only of human polymorphisms, but also of sheep, bats, whales or any other mammal. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on hypercholesterolemia.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as hypercholesterolemia. Screening each possible polymorphism in the SREBP genes represents an inventive, unpredictable and difficult undertaking in itself. As shown in the results on page 34, over 3000 human patients were studied. This would require years of inventive effort,

with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) notes with regard to association of mutations studies that larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). So the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for polymorphisms. This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example). Therefore, it is highly

unpredictable whether some currently unknown polymorphism would have any assocation with any disease.

Working Examples

The specification has a working example where two polymorphisms are associated with hypercholesterolemia.

Guidance in the Specification.

The specification did not provide sufficience evidence to demonstrate the association of any polymorphism in SEQ ID NO: 3 with hypercholesterolemia or any other disease. The specification entirely lacks any teaching or discussion of SREBP polymorphisms other than the two disclosed which are associated with hypercholesterolemia.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching gene association studies are highly unpredictable is demonstrated by Lucentini, Wacholder and Ioannidis. The specification provides one with no written description or guidance that leads one to a reliable method where an polymorphisms other than the two disclosed will be associated with hypercholesterolemia. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms as

diagnostic of hypercholesterolemia as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the full scope of the claims at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 32-36 are rejected under 35 U.S.C. 102(a) and (b) as being anticipated by Roy et al (Cell (1995) 80:167-178) as evidenced by Genbank Accession No. AC122129 and http://bacpac.chori.org/clones.htm.

Roy teaches synthesis of BAC chromosome libraries and in particular the RCPI 1 library. The RPCI library is also known as RP1, as noted at http://bacpac.chori.org/clones.htm, which states "For instance clone "RP11-103B2" indicates a clone in BAC library "RP11", a.k.a "RPCI-11". Genbank Accession No. AC122129 comprises the sequence of the RP1 clone RP1-253P7. This clone was in the RP1 library that was independently arrayed in 1995 by Roy as noted at page 176,

column 2 (and was commercially available from the BACPAC consortium). Because this clone (which is derived from human chromosome 17) teaches the complete sequence of SEQ ID NO: 3, it meets the requirements of claims 32-36.

With regard to claims 32-34, Genbank Accession No. AC122129 shows a sequence alignment

```
Genbank Accession No AC122129  69750 GCACCTAGGGAAAGGCTTC 69732
                                      |||||||||||||||||||
SEQ ID NO: 3                   1      GCACCTAGGGAAAGGCTTC 19
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With regard to claim 34, the sequence of Genbank Accession No. AC122129 inherently comprises an Xmn I site (see sequence above).

With regard to claims 35 and 36, Roy teaches that the oligonucleotide is attached, indirectly, to a solid support (see page 176, where the clones were propagated in microtiter dishes).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
12/29/08